UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,858	12/04/2001	Keith D. Allen	R-690	2822

26619 7590 09/08/2005

JOHN E. BURKE
GREENBERG TRAURIG LLP
1200 17TH STREET, SUITE 2400
DENVER, CO 80202

EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,858	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-24,27,32,33,36,38 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24,27,32,33,36 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *39* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.02

DETAILED ACTION

Claims 22-24, 27, 32-36, 38 and 39 are pending in the application. Claim 39 is withdrawn from consideration for being directed to non-elected subject matter. Claims 22-24, 27, 32-36, 38 and 39 are currently under examination.

This Office Action is in response to the Amendment filed on 6/22/05.

Response to Amendment

The rejection of claims 22-24, 27, 32, 33, 36 and 38 under 35 U.S.C. 112 1st paragraph (new matter) has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 22-24, 27, 32-36 and 38 under 35 U.S.C.101/112 1st paragraph is maintained for reasons set forth of the record mailed on 3/22/05 and further discussed below.

The specification is objected to for containing new matter.

Response to Arguments

Claims 22-24, 27, 32-36 and 38 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility.

In response to this rejection, Applicant argues that the newly amended claims, drawn to a transgenic mouse having one NTTP1 null allele, method of making and using said mouse, has patentable utility according to utility guidelines set forth in MPEP because the claimed invention has a well-established utility and is useful for a particular practical purpose. Applicant assert that the skilled in the art would immediately appreciate how to use a knockout mouse because any knockout mouse has the inherent

and well-established utility of defining the function and role of the disrupted gene regardless of specific phenotypes, characterizations or properties of the knockout mouse. Applicant further cites a passage at NIH website which indicate that knockout mice represent a critical tool in studying gene function. Furthermore, Applicant asserts that the newly amended claims drawn to a transgenic mouse comprising null-reporter alleles "is an indispensable starting point for studying the function of every gene"(Austin et al., 2004), "is an invaluable tool for investigating gene function on a genomic scale"(Molecular biology of Cell, Albert, 4th ed., Garland Science (2002), "is a powerful tool to investigate directly the importance and function of the gene" (Genes VII, Oxford university 2000), "offers a powerful approach to study gene function in a mammalian organism," (Joyner, Gene targeting: A Practical Approach, Oxford University Press 2000), "has revolutionized our ability to study gene function in cell culture *in vivo*," (Matise, Production of Targeted Embryonic Stem Cell Clones), and "provide an important means for understanding gene function."(Crawley, what's wrong with my mouse behavioral phenotype of transgenic and knockout mice, Wiley-Liss 2000). Moreover, Applicant asserts that the knockout mice have a clear, specific and unquestionable utility as with gas chromatographs, screening assays and nucleotide sequence techniques as taught by MPEP 2107.01,I. Further, Applicant asserts that studying the function of the NTTP1 is a substantial utility because there is no further research required to confirm the utility of the claimed mouse in determining NTTP1 function because 1) the value of the knockout mouse is well established in the art; 2) further characterization of the mouse itself is not required to confirm its utility in studying the NTTP1 function; 3) Applicant has provided an *in vivo* model for studying

the function of the NTTP1 gene which is associated with depression. Moreover, Applicants assert that the utility to study NTTP1 gene function and expression using the claimed mouse is specific to the NTTP1 gene knockout mouse because no other mouse can be used for this purpose. Moreover, Applicant argues that the utility of the claimed inventions does not depend on a correlation between the disclosed phenotype and a disease in human according to *In re Brana*, and the knockout mouse with a specific gene disrupted is a widely accepted model for determine gene function with well-established utility according to the teaching of Austin and Doetschman. Applicant asserts that the Federal court found that utility had been demonstrated because the claimed compound had activity against a murine tumor implanted in a mouse in *Brana*, which is similar to the instant case in which the knockout mouse with a specific gene disrupted is a widely accepted model. Applicant thus concludes that the claimed invention has credible, substantial and specific utility which satisfies the statue of 35 U.S.C. 101.

These arguments have been fully considered but deemed unpersuasive. The reasons for the utility and non-enablement rejection were discussed in detail in the office action mailed on 3/22/05 and in the utility rejection discussed above. In response to Applicant's argument regarding any knockout mouse having a well-established utility, the examiner does not agree with Applicant's assertion that the claimed invention has a well-established utility. Applicant is reminded that in the MPEP, the guideline for the utility requirement clearly states: "An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or

process), and (ii) the utility is specific, substantial, and credible." The examiner does not agree with Applicant's assertion that knockout mice have the inherent and well-established utility of defining the function and role of the disrupted gene regardless whether the inventors describe any specific phenotypes, characterizations or properties of said mouse. It is unclear how a knockout mouse without any phenotype or with transgene independent phenotype can be used to define the function of the disrupted gene. Further, such a general "inherent" utility of any knockout mouse regardless of phenotype is not specific to the instant claimed invention, a mouse having a null endogenous NTTP1 allele. It was well known to knock out a gene to determine its function or what will happen when the gene is not expressed. However, scientific "utility" is not the same as "patentable utility" or a "well-established" utility, of which must be specific, substantial and credible.. At the time of filing, knockout mice were used for further research in the art as indicated by the quotations cited by Applicant, for example, studying gene function. However, further research does not rise to the level of a "well-established utility" because such a utility is not substantial. The utility guidelines specifically state that further research is not a "substantial utility." The MPEP states "the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities": A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved..." In this case, further study of mice would have been required to determine how to use the mouse of applicant's

invention according to the embodiments described in the specification.

Applicant's assertion that the claimed mouse is useful to study the association of NTTP1 gene with the disclosed phenotype such as depression is an invitation for further research on the claimed invention in which the function of said invention Applicant clearly does not know. Further study would be required to characterize such association because the teaching of the specification is not sufficient to establish whether the phenotype is a directly result from the gene disruption. Further study would be required to determine the function of the disrupted gene and its role in the resultant phenotype. Therefore, further study would be required to determine how to use the mice to study a disorder, screening drugs and treatment for such disorder. Thus, using the mice claimed for further research is not a "substantial utility."

Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). As such, a knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using the claimed mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by

genes compensating for a knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene.

In response to Applicant's argument with regard to specific utility, Applicant is again reminded that the asserted utility of the claimed invention need to be credible, substantial and specific according to the 101 statue. The utility of studying NTTP1 function using the claimed mouse fails to meet this requirement (see reasons given above). Moreover, if the phenotype of the mouse does not result from the disruption of the gene, the association between the phenotype is not specific to the disruption of the NTTP1 gene. As such, the claimed mouse fails to meet the standard.

In response to Applicant's argument regarding using the transgenic mouse comprising null-reporter allele to study the gene expression, Applicant is reminded that studying the expression of a gene of which the function is not known is not a substantial utility. Studying the expression of a gene for the purpose of exploiting said gene function is not a substantial utility because further research is required to determine said gene function, and such gene expression pattern merely provides a clue for said gene function. The "clue" does not rise to the level of a substantial utility. Similarly, studying the expression of a gene for the purpose of determining how to use said transgenic mouse constitutes further research to determine how to use the claimed product, thus it does not provide a substantial utility to the claimed product. Therefore, the specification fails to teach a patentable utility for the claimed mouse.

In response to Applicant's argument regard *In re Brana*, the examiner does not agree that this case law applies to the instant case. In the *Brana* decision, the court concluded that the mouse tumor models (leukemia cell lines were originally derived from lymphocytic leukemia in mice) represent a specific disease against which the claimed compounds were alleged to be effective. As such, the claimed compound has credible, substantial and specific utility. In *Brana*, the asserted utility meets the requirement of the statue because the claimed compounds are effective in a valid and specific mouse tumor model. However, in the instance case, the claimed knockout mouse does not have a credible, substantial and specific use because the specification does not teach what specific disease model the claimed mouse represents and/or what type of drug the claimed mouse can screen. The mere statement that the claimed mouse can be used to study depression is not sufficient to establish a credible, substantial and specific utility for the claimed mouse. The prior art is silent on the claimed mouse thus does not recognize any well-established utility for the claimed mouse. Moreover, the utility of using the claimed mouse to study NTTP1 function or association to the phenotype is not a credible, substantial and specific utility for reasons discussed above. Therefore, unlike *Brana,* the instant specification fails to provide a credible, substantial and specific utility for the claimed mouse.

For reasons given in the previous office action and above, the specification fails to disclose a credible, substantial and specific use for the claimed mouse and one skilled in the art would not know how to use the claimed mouse according to the embodiments

disclosed by the instant specification. Since the claimed mouse does not have patentable utility, the method of making said mouse and cells or tissues obtained from said mouse do not have patentable utility either.

Claims 22-24, 27, 32-36 and 38 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In response to this rejection, Applicant argues that the claimed invention satisfied the enablement requirement because the specification teaches how to make and use the mouse. Applicant asserts that there is no requirement to recite the phenotype in the claims because the phenotype is an inherent property to the mouse. Applicant argues that the phenotype of the mouse with null mutation is predictable so that all the mouse with null allele of NTTP1 would have the same phenotype. Applicant asserts that phenotypes associated with the disruption of the NTTP1 are inherent to the mouse whereas phenotypes not associated the disruption are "transgene independent" phenotypes for which the claimed mouse also possesses. Applicant argues that Crawley is not sufficient to support Examiner's assertion because it does not recommend that investigators discontinue use of any strain including C57BL/6 and 129 used by Applicant. Applicant further asserts that Olsen is unsupportive of the Examiner's position that the phenotype of the claimed mouse may be the result of compensation by other genes, citing statements such as "the use of mutant and knockout mice has

aided understanding of the roles of GAD and GABAR in the intact mammalian organism," "transgenic and knockout mice have demonstrated that GABA plays a role in brain development, control of palate formation..." Applicant thus concludes that the invention is enabled by the instant specification.

Applicant's argument has been fully considered but deemed unpersuasive. The reasons for non-enablement of the claimed invention were discussed in detail in the previous office actions. With regard to Applicant's argument of predictability of phenotype, although Applicant use gender, age and strain matched wild type controls, the phenotype of a mutant mouse is not only the result of the targeted gene, but it also reflects interactions with background genes, and other unknown mutations in the genetic background (see Crawley, pages 107 last paragraph through page 108 1st paragraph). Since C57BL/6 and various substrains of 129, two strains commonly used in ES cell and knockout generation, are unusual on many standard behavioral paradigms (see page 108, 2nd paragraph), (which are also used by Applicant for generating the NTTP1 domain gene knockout mouse), further characterization is required to make sure that the claimed phenotype truly resulted from the inhibition of the NTTP1 domain gene. Although making a mouse with a null allele by a replacement vector usually knocks out the gene, the phenotype is still unpredictable because it not only depends on the function of the endogenous gene but also what exogenous DNA the gene is inserted/replaced with, and where the exogenous DNA is inserted (see Scarff et al., 2003, Genesis, Vol. 36, page 149-157, specifically page 155, 1st col., 3rd paragraph). The specification does not teach

how to distinguished between the claimed phenotype of which are so called "inherent" and "transgene independent." As such, further research is clearly required to determine which phenotype directly results from the NTTP1 gene disruption. Otherwise, one skilled in the art would not know how to use the claimed invention according to embodiments taught by the specification. Since the Examiner has never stated that Crawley et al. suggests discontinued use of certain strains of mice, Applicant's rebuttal with regard to this notion is thus moot.

In response to Applicant's argument with regard to the requirement of reciting a phenotype, Applicant is reminded that according to the statue of 112 1st paragraph, critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The phenotype of the claimed mouse is critical or essential to for using the knockout mouse; therefore, need to be recited in the claim. The examiner does not agree that the phenotype is an inherent property of the claimed mouse because the phenotype of the mouse is unpredictable for reasons discussed in the previous office action and above. One skilled in the art would not know how to use the knockout mouse without any phenotype.

In response to Applicant's argument with regard to Olsen, Applicant is reminded that quoting passages that teaches the utility of other knockout mouse does not give utility to the claimed knockout mouse. As discussed in the utility rejection, this reference teaches that knockout mice may not be capable of elucidating the function of the protein which is knocked out, and may only provide a clue to a pathway the protein being

knocked out is involved in. Thus, it added unpredictability to whether the phenotype of the claimed mouse directly results from the lack of function of the NTTP1 gene. Contrary to Applicant's assertion, whether the phenotypes directly result from the null allele is rather critical to the utility of the claimed mouse. If the phenotype is transgene independent, any agent that affects this phenotype would have nothing to with the NTTP1 function. Further, said mouse with a transgene independent phenotype clearly does not provide any information to the function of the gene being knocked out. Moreover, if the phenotype of the mouse does not directly result from the disruption of the gene, the association between the phenotype is not specific to the disruption of the NTTP1 gene, thus it fails to meet the utility requirement (see discussion above). The Examiner is not responsible to find out what genes contribute to the claimed phenotype. The burden is on the Applicant to provide sufficient teaching in the specification for a credible, substantial and specific use for the claimed invention, and sufficient teaching for how to use the claimed invention according to the disclosed embodiments. For reasons discussed in the previous office action and above, this rejection is thus maintained.

Specification

The amendment filed 3/4/05 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The original specification discloses "a targeting construct prepared directly from a plasmid library using the methods described in pending U.S. Patent Application Ser No.: 08/971,310, filed on November 17, 1997, the disclosure of which is incorporated herein in its entirety." The amendment

filed on 3/4/05 amended the language to "using the methods described in U.S. Patent no. 6,815,185 issued November 9, 2004, which is based on U.S. Patent No. 09/885,816...which is incorporated herein in its entirety." Such amendment introduces new matter because the disclosure of "U.S. Patent no. 6,815,185 issued November 9, 2004, which is based on U.S. Patent No. 09/885,816..." differs from the original disclosure and contains new information which was not disclosed in the original specification. Therefore, such amendment contains new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER